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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/636,519	08/10/2000	Jacques P. Dumas	5051	6414

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EXAMINER
BALASUBRAMANIAN, VENKATARAMAN

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 02/26/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/636,519	DUMAS ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-19 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-19 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election of Group II, claims 1-19, in Paper No. 6 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-19 will be examined to the extent they embrace the elected subject matter.

Claims 1-19 are pending in the case.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following apply. Any claim not specifically rejected is rejected as it dependent on a rejected claim.

1. Recitation of the term "generalized" in claims 1-3, 7-9 and 13-15 render the claims vague and indefinite as the term implies more than what is being positively recited therein. Its deletion is suggested.
2. Recitation of the phrase " wherein binding is achieved via the terminal carbon atoms" in claims 1-3, 7-9 and 13-15 render these claims indefinite for more than one reason. First of all, the term "binding" means physical process not synonymous with "bonding". Furthermore, it is not clear what are these terminal

carbon atoms, as R^1 and R^2 are not defined properly to indicate that they have terminal carbon atoms. An appropriate correction is needed.

3. Claims 1-3,7-9 and 13-15 recite at various places the term "containing" which renders the these claims indefinite. The transitional term "containing," which is synonymous with "including," or "comprising", "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. "Containing" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim "comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts". See MPEP 2111.03.

4. Claims 6, 12 and 18 recite the term "including" which render these claims indefinite for the same reason # 3. Note the term is open-ended term can include more than what is being positively recited therein.

5. Claims 5, 11 and 17 are deemed as indefinite as they recite the phrase " a condition characterized by abnormal angiogenesis" for more than one reason. First of all, it is not clear what is this "condition". Specification has no definition of this term. Furthermore it is not clear what conditions are due to abnormal angiogenesis and normal angiogenesis.

6. In claim 19, the species u) is outside the scope of elected subject matter.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-6,11-12 and 17-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for angiogenesis and treatment of related tumor growth and retinopathy, does not reasonably provide enablement for any or all conditions including those yet to be discovered as due angiogenesis, particularly abnormal angiogenesis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to "treating a mammal having a condition characterized by "abnormal angiogenesis" .The scope of the claims includes not only any or all conditions but also those condition yet to be discovered as due to "abnormal angiogenesis" for which there is no enabling disclosure. In addition, the scope of these claims includes treatment of various diseases, which is not adequately enabled solely based on the activity of the compounds provided in the specification at pages 55-56. The instant compounds are disclosed to have KDR kinase inhibitory activity which relates to inhibition of VEGF and it is recited that the instant compounds are therefore useful in treating any or all conditions, for which applicants provide no competent evidence. In addition there is no teaching and there is no evidence of record which would enable the skilled artisan in the identification of the people who would have abnormal angiogenesis related condition claimed herein. It appears that the applicants

are asserting that the embraced compounds because of their mode action as KDR kinase inhibitor that would be useful for all sorts of diseases including all inflammatory diseases such as rheumatoid arthritis, psoriasis, immune diseases, atherosclerosis, degenerative disease such as age-related macular degeneration etc. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of diseases such as rheumatoid arthritis, psoriasis and macular degeneration are very difficult to treat and at present there is no known drug, which can successfully reverse the course of these diseases, despite the fact that there are many drugs, which can be used for "inflammatory condition". Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses. Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. (Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements). The state of the art is indicative of the requirement for undue experimentation. See Jayson (Pub Med

Abstract), which suggest that current status at best exploratory and need further experimentation. In addition, based on the claim language, it appears that applicant's compounds are effective for "abnormal angiogenesis" as compare to "angiogenesis ". Specification has no teaching as to this as assays relied upon are for angiogenesis or related vascular permeability inhibition via KDR kinase inhibition.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating diseases that require abnormal angiogenesis inhibitory activity.

2) The state of the prior art: A very recent publication expressed that the VEGF antagonist effects are unpredictable and are still exploratory.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for r treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all condition and the state of the art is that the effects of KDR kinase/VEGF inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace any or all condition including those yet to be related to angiogenesis.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards 'preventing' the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application

by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-19 are rejected under 35 U.S.C. 102(e) as being anticipated by Bold et al. US 6,258,812.

Bold et al. teaches several phthalazines with angiogenesis activity, which include compounds claimed in the instant claims. See formula I on col. 3 and note the definition of various groups. Note the definition of N-containing A-B-D-E ring corresponds to instant A-B-D-E-L ring, Q corresponds to instant G, G corresponds to instant Y, X corresponds to instant J. particularly note when Y is aryl the substituents permitted includes those claimed in the instant claims for G^4 group. See col. 4 through col. 17 for

details and preferred embodiments and col. 18-34 for process of making these compounds. Also see col. 34-81 for examples of compounds made including the tables shown therein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bold et al. US 6.258,812.

Teachings of Bold et al. as discussed in the above 102 rejection is incorporated herein. As noted above Bold et al. teaches several phthalazine compounds for treating angiogenesis.

The instant claims differ from the reference in requiring variously substituted compounds with substituents in the phthalazine ring, heterocyclic ring A-B-D-E-L ring, and J ring. Furthermore, claim 19 requires specific species. Bold et al. as noted in examples shown on col. 34-81 teaches variously substituted phthalazines but not all claimed in the instant claims.

However, Bold et al. teaches the equivalency of exemplified substituted phthalazines shown in examples and the tables stated above with phthalazines with variously substituted in aryl ring, N-A-B-D-E ring and the aryl ring of the phthalazine ring claimed in the definition of compound of formula I. See cols. 1 through col. 17. Thus, it

would have been obvious to one having ordinary skill in the art at the time of the invention was made would have been to make compounds variously substituted phthalazine and aryl and N-A-B-D-E rings as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (703) 305-1674. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 5.30 PM.

The fax phone number for the organization where this application or proceeding is assigned (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

V. Balasubramanian
Venkataraman Balasubramanian

2/21/2002